- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a pattern of chronic inflammation induced by T cell and macrophage activation in response to an agent that is resistant to eradication.

Systemic Effects of Inflammation

Inflammation, even if it is localized, is associated with cytokine-induced systemic reactions that are collectively called the *acute-phase response*. Anyone who has suffered through a severe bout of a viral illness (e.g.., influenza) has experienced the systemic manifestations of acute inflammation. These changes are reactions to cytokines whose production is stimulated by bacterial products such as LPS and by other inflammatory stimuli. **The cytokines TNF, IL-1, and IL-6 are important mediators of the acute-phase reaction; other cytokines, notably type I interferons, also contribute to the reaction.**

The acute-phase response consists of several clinical and pathologic changes:

- **Fever,** characterized by an elevation of body temperature, usually by 1° to 4°C, is one of the most prominent manifestations of the acute-phase response, especially when inflammation is associated with infection. Substances that induce fever are called *pyrogens.* The increase in body temperature is caused by prostaglandins that are produced in the vascular and perivascular cells of the hypothalamus. Bacterial products, such as LPS (called *exogenous pyrogens*), stimulate leukocytes to release cytokines such as IL-1 and TNF (called *endogenous pyrogens*) that increase the enzymes (cyclooxygenases) that convert AA into prostaglandins. In the hypothalamus, the prostaglandins, especially PGE_2, stimulate the production of neurotransmitters that reset the temperature set point at a higher level. NSAIDs, including aspirin, reduce fever by inhibiting prostaglandin synthesis. An elevated body temperature has been shown to help amphibians ward off microbial infections, and it is assumed that fever is a protective host response in mammals as well, although the mechanism is unknown. One hypothesis is that fever may induce heat shock proteins that enhance lymphocyte responses to microbial antigens.
- **Acute-phase proteins** are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli. Three of the best-known of these proteins are C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein. Synthesis of these molecules in hepatocytes is stimulated by cytokines, especially IL-6 (for CRP and fibrinogen) and IL-1 or TNF (for SAA). Many acute-phase proteins, such as CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement. They also bind chromatin, possibly aiding in clearing necrotic cell nuclei. Fibrinogen binds to red cells and causes them to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual red cells. This is the basis for measuring the *erythrocyte sedimentation rate* as a simple test for an inflammatory response caused by any stimulus. Acute-phase proteins have beneficial effects during acute inflammation, but prolonged production of these proteins (especially SAA) in states of chronic inflammation causes *secondary amyloidosis* (Chapter 6). Elevated serum levels of CRP have been proposed as a marker for increased risk of myocardial infarction in patients with coronary artery disease. It is postulated that inflammation involving atherosclerotic plaques in the coronary arteries may predispose to thrombosis and subsequent infarction. Another peptide whose production is increased in the acute-phase response is the iron-regulating peptide *hepcidin*. Chronically elevated plasma concentrations of hepcidin reduce the availability of iron and are responsible for the *anemia* associated with chronic inflammation (Chapter 14).
- **Leukocytosis** is a common feature of inflammatory reactions, especially those induced by bacterial infections. The leukocyte count usually climbs to 15,000 or 20,000 cells/mL, but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/mL. These extreme elevations are referred to as *leukemoid reactions*, because they are similar to the white cell counts observed in leukemia and have to be distinguished from leukemia. The leukocytosis occurs initially because of accelerated release of cells from the bone marrow postmitotic reserve pool (caused by cytokines, including TNF and IL-1) and is therefore associated with a rise in the number of more immature neutrophils in the blood, referred to as a *left shift*. Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of colony-stimulating factors. Thus, the bone marrow output of leukocytes is increased to compensate for the loss of these cells in the inflammatory reaction. (See also the discussion of leukocytosis in Chapter 13.) Most bacterial infections induce an increase in the blood neutrophil count, called *neutrophilia*. Viral infections, such as infectious mononucleosis, mumps, and German measles, cause an absolute increase in the number of lymphocytes *(lymphocytosis)*. In some allergies and parasitic infestations, there is an increase in the absolute number of eosinophils, creating an *eosinophilia*. Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells *(leukopenia)*.
- Other manifestations of the acute-phase response include increased pulse and blood pressure; decreased sweating, mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin; rigors (shivering), chills (search for warmth), anorexia, somnolence, and malaise, probably because of the actions of cytokines on brain cells.
- In severe bacterial infections *(sepsis),* the large amounts of bacteria and their products in the blood stimulate the production of enormous quantities of several cytokines, notably TNF and IL-1. High blood levels of cytokines cause various widespread clinical manifestations such